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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

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DAHLE, CHUN WU	
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte RONIT EISENBERG and TAMAR RAZ

Appeal 2009-014852
Application 10/009,809
Technology Center 1600

Decided: April 26, 2010

Before ERIC GRIMES, DONALD E. ADAMS, and STEPHEN WALSH, *Administrative Patent Judges*.

GRIMES, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method to "reduce or abolish mast cell degranulation, and in particular to reduce or abolish allergy mediators such as histamine secretion from mast cells" (Spec. 1: 6-8). The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF THE CASE

"[M]ast cells are significant contributors to the allergic reaction and are packed with 500 to 1000 granules in which the mediators of the inflammatory reactions are stored. These include vasoactive mediators such as histamine." (Spec. 1: 18-20.) "Mast cells secrete their granular contents in a process of regulated exocytosis (degranulation)" (*id.* at 2: 25 to 3: 1).

Claims 63-70 and 72-78 are on appeal. The claims subject to each rejection have not been argued separately and therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii). Claim 63 is representative and reads as follows:

63. A method of inhibiting mast cell degranulation in a subject, the method comprising administering to the subject a pharmaceutically effective amount of a therapeutic agent, wherein said therapeutic agent comprises a complex molecule which comprises a first segment having an amino acid sequence AAVALLPAVLLALLAP (SEQ ID NO: 3) linked via a linker to a second segment having an amino acid sequence KNNLKECGLY (SEQ ID NO: 1), thereby inhibiting mast cell degranulation in the subject.

I.

Issue

The Examiner has rejected claims 63, 66-70, and 72-78 under 35 U.S.C. § 103(a) as obvious in view of Holgate,[1] Aridor,[2] and Lin[3] (Ans. 4). The Examiner has also rejected claims 64 and 65 as obvious in view of

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[1] S. T. Holgate et al., "*THE MAST CELL*," 48 (no. 1) BRITISH MEDICAL BULLETIN 40-50 (1992).
[2] Meir Aridor et al., "*Activation of Exocytosis by the Heterotrimeric G Protein G_{i3}*," 262 SCIENCE 1569-1572 (1993).
[3] Lin et al. US 5,807,746, Sept. 15, 1998.

Holgate, Aridor, Lin, Avruch,[4] and Jackson[5] (Ans. 6). Because the same issue is dispositive with respect to both rejections, we will consider them together.

The Examiner finds that Holgate teaches that "agents that can suppress the release of mast cell mediators have been shown to be clinically effective in treating asthma" (Ans. 4), Aridor teaches that the "peptide KNNLKECGLY . . . inhibits permeabil[i]zed mast cell degranulation" (*id.*), and Lin teaches that the peptide "AAVALLPAVLLALLAP . . . is a useful signal peptide that is capable of translocating biologically active molecules across the cell membrane" (*id.* at 5). The Examiner concludes that it would have been obvious to combine the peptides taught by Aridor and Lin because doing so would provide a peptide that would be imported into mast cells and inhibit their degranulation (*id.*).

Appellants contend that the evidence shows that, out of four cell-penetrating peptides, only the peptide of SEQ ID NO: 3 inhibited mast cell degranulation when fused to an appropriate second peptide. Appellants contend that this result shows unpredictability that casts doubt on the expectation of success in combining the references, or alternatively shows surprising results that rebut a prima facie case of obviousness (Appeal Br. 6-10).

The issue presented is: Does the evidence of record support the Examiner's conclusion that a person of ordinary skill in the art would have

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[4] Avruch et al., US 6,103,692, Aug. 15, 2000.
[5] Sharon Jackson et al., *"Template-Constrained Cyclic Peptides: Design of High-Affinity Ligands for GPIIb/IIIa,"* 116 J. AM. CHEM. SOC. 3220-3230 (1994).

reasonably expected that combining Aridor's peptide with Lin's signal peptide would result in a fusion peptide that inhibits mast cell degranulation?

Findings of Fact

1. Lin discloses that "importing exogenous biologically active molecules into intact cells can be engineered by forming a complex by attaching an importation competent signal peptide sequence to a selected biologically active molecule and administering the complex to the cell. The complex is then imported across the cell membrane." (Lin, col. 3, ll. 28-34.)

2. Lin discloses that "[e]xamples of biologically active molecules include proteins, polypeptides and peptides" (*id.* at col. 3, ll. 61-62).

3. Lin discloses that "a useful signal peptide is the signal peptide from Kaposi fibroblast growth factor (K-FGF), listed herein as SEQ ID NO:5" (*id.* at col. 7, ll. 13-15, reference citations omitted).

4. Lin's SEQ ID NO: 5 is the same amino acid sequence as SEQ ID NO: 3 of the present application.

5. Lin discloses that "[a]ny selected cell into which import of a biologically active molecule would be useful can be targeted by this method, as long as there is a means to bring the complex in contact with the selected cell. . . . [T]he cell can be targeted by, for example, inhalation of the molecule linked to the peptide to target the lung epithelium." (*Id.* at col. 8, ll. 24-31.)

6. Lin discloses that "any selected signal peptide can be routinely tested for the ability to translocate across the cell membrane of any given cell type according to the teachings herein" (*id.* at col. 6, ll. 57-60).

7. Aridor discloses the effects of two peptides on mast cell exocytosis: "Permeabilized cells were exposed to various concentrations of

the synthetic peptides KE and EC. . . . The KE peptide at concentrations of up to 100 μg/ml had no effect on histamine secretion. . . . In contrast, the EC peptide inhibited secretion." (Aridor 1570, left col.)

8. Aridor's EC peptide has the same amino acid sequence as the present application's SEQ ID NO: 1 (Aridor 1571, note 21).

9. Aridor discloses that the "EC peptide was ineffective when added to intact cells, indicating that the target for the peptide was intracellular" (*id.* at 1570, left col.).

10. Holgate discloses that "mast cells, . . . when primed and activated, [are] effector cells of acute bronchoconstriction in asthma" (Holgate, 40).

11. Holgate discloses that "[s]uppression of mast cell mediator release has been used to explain the clinical efficacy of [asthma] drugs such as sodium cromoglycate and nedocromil sodium" (*id.* at 47).

12. The Specification discloses that one approach to introducing a peptide into cells

> is based on the fusion of the selected peptide with a specific hydrophobic sequence, comprising the 'h' region of a signal peptide sequence. Examples of such hydrophobic regions are the signal sequence of the Kaposi fibroblast growth factor . . . and the signal sequence within human integrin β_3 . . . [or] a specific signal peptide sequence endowed with the membrane translocation properties of the homeodomain of Antennapedia, a *Drosophila* transcription factor.

(Spec. 4: 19 to 5: 1.)

13. The Specification discloses that two fusion peptides that include the Kaposi fibroblast growth factor signal sequence inhibited histamine secretion from activated mast cells (*id.* at 13: 7-22; peptides 2 and 5).

14. The Specification discloses that four fusion peptides that include the signal sequence from either human integrin β_3 or *Drosophila*

Antennapedia did not inhibit histamine release from activated mast cells (*id.*, peptides 1, 3, 4, and 6).

Principles of Law

"One way for a patent applicant to rebut a *prima facie* case of obviousness is to make a showing of 'unexpected results,' *i.e.*, to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

"[B]y definition, any superior property must be *unexpected* to be considered evidence of non-obviousness. Thus, in order to properly evaluate whether a superior property was unexpected, the [fact-finder] should . . . consider[ ] what properties were expected." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007).

Analysis

Claim 63 is directed to a method of inhibiting mast cell degranulation by administering, for example, a fusion peptide comprising the peptide of SEQ ID NO: 3 (the KFGF signal peptide) linked to the peptide of SEQ ID NO: 1.

Aridor discloses that the peptide of SEQ ID NO: 1 inhibits release of histamine from mast cells (i.e., degranulation) by interacting with an intracellular target. Lin discloses that the KFGF signal peptide transports an attached peptide into intact cells. We agree with the Examiner that a person of ordinary skill in the art would have considered it obvious to fuse the peptides disclosed by Aridor and Lin and to administer the fusion peptide to a subject to inhibit mast cell degranulation, since Holgate discloses that

release of mediators from activated mast cells contributes to the acute bronchoconstriction seen in asthma patients.

Appellants argue that the evidence of record shows that only one out of four cell-penetrating peptides successfully delivered a biologically active inhibitor of mast cell degranulation (Appeal Br. 6-7). Appellants argue that this result indicates that the Examiner's rejection is not supported by a reasonable expectation of success, or alternatively that Appellants have provided surprising results that overcome the rejection (*id.*). In support of their position, Appellants point to declarations that were submitted under 37 C.F.R. § 1.132 by Dr. Ehud Razin and Dr. Ronit Eisenberg (*id.* at 7-8).

This argument is not persuasive. The claims on appeal are directed to agents that include the KFGF signal sequence. The issue that is relevant to the Examiner's rejections, therefore, is whether a person of ordinary skill in the art would have expected the *KFGF signal sequence* to effectively direct the importation of an attached peptide into mast cells.

Lin discloses that the KFGF signal peptide directs importation of an attached peptide (FFs 1-3) into any selected cell the fusion peptide is brought into contact with (FF 5). Appellants have pointed to no evidence in the record that contradicts Lin's statement that the KFGF signal peptide predictably directs importation of an attached peptide into cells. And, as the Examiner has pointed out (Answer 9), Lin discloses that signal peptides can routinely be tested for ability to translocate across the membrane of different cell types (FF 6). Appellants have not provided an adequate basis on which to conclude that Lin would not have provided a person of ordinary skill in the art with a reasonable expectation of success for the claimed invention.

Appellants point to evidence that signal peptides from human integrin β_3, *Drosophila* Antennapedia, and "TP-10" did not direct importation of a functional peptide into mast cells (Appeal Br. 7-8, Reply Br. 1-2; Razin and Eisenberg declarations, ¶¶ 7, 8). Appellants have not, however, adequately explained why the failure of other signal peptides would have led a skilled worker to doubt Lin's statement that the *KFGF signal peptide* directs importation of an attached peptide into cells.

The fact that other signal peptides did not work doesn't change the fact that Lin would have led a skilled worker to expect the KFGF signal peptide to work in the method suggested by the cited references; whether something outside the scope of the claims worked less well than might have been expected is not relevant to the patentability of the claimed method. Appellants have not shown that fusion proteins that include the KFGF signal peptide have unpredictable properties, or that using the KFGF signal peptide provides unexpectedly superior results compared to what would have been expected *for that peptide* based on the prior art.

Conclusion of Law

The evidence of record supports the Examiner's conclusion that a person of ordinary skill in the art would have reasonably expected that combining Aridor's peptide with Lin's signal peptide would result in a fusion peptide that inhibits mast cell degranulation.

SUMMARY

We affirm the rejection of claims 63, 66-70, and 72-78 under 35 U.S.C. § 103(a) based on Holgate, Aridor, and Lin, and the rejection of claims 64 and 65 based on Holgate, Aridor, Lin, Avruch, and Jackson.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO CA 94111-3834